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UNITED STATES DISTRICT COURT

FOR THE CENTRAL DISTRICT OF CALIFORNIA

EASTERN DIVISION

UNITED STATES OF AMERICA,

Plaintiff,

v.

CALIFORNIA STEM CELL TREATMENT CENTER, INC., *et al.*

Defendants.

No. 5:18-CV-01005-JGB-KKx

PLAINTIFF'S SUPPLEMENTAL MEMORANDUM REGARDING THE DEFINITION OF AN HCT/P, 21 C.F.R. § 1271.3(d)

Trial: May 4 – 13, 2021

Honorable Jesus G. Bernal
United States District Judge

The Government submits this supplemental memorandum regarding the Court's question why—as a matter of statutory construction—Defendants should not be excepted from regulation under Defendants' interpretation of the definition of human cells, tissues, or cellular or tissue-based products ("HCT/Ps"). Defendants are not excepted from regulation because, under canons of statutory construction and through careful parsing of the regulatory text and history, adipose tissue is an HCT/P. Even if the Court were to regard certain, varied cellular components of adipose tissue (*i.e.*, SVF) to be the HCT/P removed here, Defendants would not qualify for an exception because the cells change after they are removed, rendering them no longer "such HCT/P." Any other reading would allow a narrowly crafted exception to swallow the regulation and upset FDA's carefully balanced, risk-based approach designed to protect the public health.

1. The Definition of an HCT/P is Broad and Applies to Both Cells and Tissues

Under Section 1271.3(d), HCT/P means "articles containing or consisting of human cells or tissues that are intended for implantation . . . into a human recipient." Pursuant to several canons of construction, the limiting phrase "that are intended for implantation . . ." immediately follows and therefore applies to "cells or tissues" and not to "articles."[1] The term "article" is not defined in Part 1271, but adds consistency with definitions found elsewhere in the FDCA. *See, e.g.*, 21 U.S.C. §§ 321(f) & (g) (defining food and drug).

[1] For instance, under the "rule of the last antecedent," a "limiting clause or phrase . . . should ordinarily be read as modifying only the noun or phrase that it immediately follows." *Barnhart v. Thomas*, 540 U.S. 20, 26 (2003); *see also Lockhart v. United States*, 577 U.S. 347, 351-52 (2016); Scalia & Garner, Reading Law: The Interpretation of Legal Texts 144-46 (2012). The first part of the definition ("articles containing or consisting of human cells or tissue") is not a single integrated list and the term "human cells or tissues" is separated structurally from the term "articles." The "intended" modifier could only apply to "articles" by leapfrogging over "cells or tissues." No structural or contextual indicia exists to overcome the rule. *See Lockhart*, 577 U.S. at 355; *Jama v. ICE*, 543 U.S. 335, 344, n.4 (2005). Reading the definition in context with Part 1271 as a whole, the definition applies not just to the SSPE but to a litany of other regulatory provisions that govern the listing, manufacture, and storage of HCT/Ps. *See* 21 C.F.R. § 1271.3 (explaining that the Part 1271 definitions apply throughout that Part); 66 Fed. Reg. 5447, 5448 (Jan. 19, 2001) ("The definition of 'human cells, tissues, or cellular or tissue-based product' is intended to cover HCT/P's at all stages of their manufacture, from recovery through distribution."). *Cf. Hall v. United States Dep't of Agric.*, 984 F.3d 825, 837-38 (9th Cir. 2020) (discussing application of "nearest-reasonable-referent" canon).

Parsing the provisions of Section 1271.3(d) shows that four types of articles may qualify as HCT/Ps, namely those: (1) containing *cells* intended for implantation; (2) containing *tissues* intended for implantation; (3) consisting of *cells* intended for implantation; and (4) consisting of *tissues* intended for implantation. Thus, the removed adipose tissue (an article containing cells intended to be implanted) and the SVF cellular fraction derived from adipose tissue (an article consisting of various types of cells intended to be implanted) are both HCT/Ps under different provisions of the definition.[2] Since an article must fall within a specific provision of the definition to be considered an HCT/P, it stands to reason that when interpreting other sections of the regulatory text referring to HCT/Ps, such as the same surgical procedure exception ("SSPE"), it is important to consider the particular provision of the HCT/P definition that was met.

2. The Text of the SSPE Precludes the Defendants' Proposed Interpretation

By including the term "such HCT/P's," the text of 1271.15(b) compares the type of HCT/P removed to the type of HCT/P to be implanted. The term "such" is generally defined as "[t]hat or those; having just been mentioned." *Such*, Black's Law Dictionary (17th ed.) at 1446. Expanding the definition of an HCT/P in the SSPE to reflect the provision under which the article qualified as an HCT/P shows, as a matter of statutory construction, that if an article containing *cells* intended for implantation is removed, "such" article containing *cells* must be reimplanted for the SSPE to apply. Conversely, if an article containing *cells* intended for implantation is removed, an article only consisting of *cells* intended for implantation cannot qualify for the SSPE because it is not "such HCT/P." Under the plain language of Part 1271, Defendants cannot qualify for the SSPE by removing adipose tissue and implanting SVF, expanded SVF, or SVF/Vaccinia.

[2] This is consistent with the Eleventh Circuit's decision in *United States v. U.S. Stem Cell Clinic*, 998 F.3d 1302, 1308 (11th Cir. 2021) ("The adipose tissue contains the stromal-vascular fraction, which consists of cells intended for implantation into a patient. Therefore, both adipose tissue and stromal-vascular fraction are HCT/Ps."). To the extent there is any ambiguity, it should be resolved in favor of FDA's considered expert judgment in a way that protects the public health. *See Kisor v. Wilkie*, 139 S. Ct. 2400, 2415-16 (2019); *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994),

Any assertion that it is not "scientifically possible" to remove the collection of various cell types in the SVF product from an individual is not evidence of any flaw or "paradox" in the regulation; if an HCT/P consisting of cells can be removed, such HCT/P consisting of cells can be implanted under the SSPE.[3] Defendants' inability to do so without removing and extensively processing adipose tissue is no fault of the regulation and certainly not a valid basis for creating a brand new regulatory exception based purely on what is *intended* to be implanted—especially in light of the many establishments that can and do remove HCT/Ps and implant such HCT/Ps in compliance with the SSPE. The refusal to comply with a regulation is no "paradox," it is simply violative conduct.

3. The Proposed Interpretation Would Lead to An Absurd Result

Under the proposed interpretation, an establishment could remove *any* type of HCT/P from *any* part of a patient, perform *any* number and type of manufacturing steps on that tissue in relation to *any* purported surgical procedure (regardless of the risk associated with any of those steps), inject the end product into *any* part of the patient, and then invoke the SSPE as long as the end product contained unchanged cells that the establishment *intended* to implant. This interpretation, whereby nearly all autologous HCT/Ps may qualify for the narrow SSPE, could result in untold harm to patients.

4. Evidence Admitted at Trial Supports the Government's Textual Argument

Although the textual analysis above is a gross oversimplification of the scientific and fact-intensive inquiry that FDA undertakes when evaluating the SSPE, it is entirely consistent with both the evidence admitted at trial and FDA's decades-old regulation of tissue in a manner protecting the public health. Trial testimony and exhibits showed the HCT/P implanted is plainly not the "such HCT/P" removed. Defendants' manufacturing fundamentally changes the adipose tissue. Indeed, to obtain SVF, Defendants necessarily

[3] Defendants are incorrect to suggest that the Government's interpretation means that cells could never qualify for the SSPE because they are always removed from a larger system, even though the definition of HCT/P includes cells. It *is* possible to remove cells from an individual without removing other parts of the individual's body (*e.g.*, an ovocyte/oocyte). Pl.'s Prop. FOF/COL, ECF No. 169-1, at 63 n.33.

destroy the adipose tissue removed from the patient, converting it into an entirely different product. Defendants do not implant "such HCT/P." *See* Pl.'s Tr. Br., ECF No. 151, at 18-19; Pl.'s Prop. FOF/COL, ECF No. 169-1, at 15-16, 61-67.

Even if, contrary to the Government's interpretation, adipose tissue is not considered an HCT/P because it is not "intended" for implantation, the SSPE would still be inapplicable. Specifically, if only the cells themselves are considered the antecedent for the SSPE analysis, the HCT/P implanted is still not "such HCT/P" that was removed. As established at trial, SVF is not naturally occurring. The cells undergo Defendants' extensive processing, which changes the cells both physically and biologically, including changes to the cells' morphology, surface marker expression, and activation state. Pl.'s Prop. FOF/COL, ECF No. 169-1, at 16-24. These changes necessarily affect cellular processes, metabolic activity, and the ability to mediate the behavior of other cells. *Id.*

Further, there can be no question that the expanded SVF and the SVF/Vaccinia products are not the "such HCT/P's" that were removed from the patient. The expanded SVF product contains cells replicated from the patient's original cells in a laboratory culture. This is in no way the "such HCT/P" removed from the individual. *See* Pl.'s Prop. FOF/COL, ECF No. 169-1, at 8-9, 48-50. Similarly, to manufacture the SVF/Vaccinia product, Defendants combine SVF derived from a patient's adipose tissue with a live virus vaccine labeled with FDA's most severe warning. *See* Pl.'s Prop. FOF/COL, ECF No. 169-1, at 39-40. The SVF/Vaccinia product that Defendants administer to patients is neither the adipose tissue removed from the patient nor "such HCT/P." Defendants have therefore not carried their burden to show the SSPE applies to any of the three SVF products at issue in this case. *See* 21 C.F.R. § 1271.15(b); *United States v. Regenerative Scis.*, 741 F.3d 1314, 1322 (D.C. Cir. 2014) (citing *United States v. First City Nat'l Bank of Houston*, 386 U.S. 361, 366 (1967)).

5. An Expansive View of The SSPE Is Inconsistent With Public Health Protections

The proposed interpretation would also have negative real-world implications for

the regulation of drugs nationwide. Under the FDCA, FDA regulates articles (including autologous cellular products, *e.g.*, SVF products) intended to treat human disease as biological "drugs" under a tiered, risk-based approach. *See* 21 C.F.R. § 1271.15(b); *see also Regenerative Scis.*, 741 F.3d at 1319-20. From the beginning, FDA has been clear that the SSPE applies only in limited circumstances[4] where risks would generally be no different than those typically associated with surgery, such as autologous skin grafting or coronary artery bypass surgery of autologous veins or artery grafting. *See* Pl.'s Tr. Br., ECF No. 151, at 19-21.

Here, Defendants attempt to extend the SSPE well beyond its very narrow scope to encompass HCT/Ps that pose risks far greater than those typically associated with surgery. Defendants remove a patient's adipose tissue and then *introduce an enzyme solution that chemically digests the tissue and alters the cells within it*. After additional processing, Defendants add saline to create an SVF product. Defendants create two other products by performing additional steps to either replicate the patient's cells in culture or add SVF to excessive amounts of *a live virus* vaccine before administration. Defendants' extensive processing greatly enhances risk and introduces new dangers. Their manufacturing processes do not resemble the surgical procedures covered by the SSPE.

As discussed, the SSPE is a very narrow exception intended to ensure that FDA regulation does not unnecessarily infringe on traditional surgical procedures. An expansive interpretation of the SSPE could undermine important public health protections and allow the narrow SSPE to entirely swallow FDCA's drug approval process for any product manufactured from a patient's HCT/P.

CONCLUSION

Defendants are not excepted from regulation under 21 C.F.R. Part 1271 pursuant to any reading of 21 C.F.R. §§ 1271.3(d) or 1271.15(b).

[4] Exceptions from the law, especially exceptions to a public health law, should be narrowly construed. *See United States v. Kanasco, Ltd*, 123 F.3d 209, 211-12 (4th Cir. 1997), *citing Spokane & Inland Empire R.R. v. United States*, 241 U.S. 344, 350, 60 L. Ed. 1037, 36 S. Ct. 668 (1916).

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Respectfully Submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on this 27th day of August 2021, I electronically filed a true and correct copy of the foregoing PLAINTIFF'S SUPPLEMENTAL MEMORANDUM REGARDING THE DEFINITION OF HCT/P through the Court's CM/ECF system, which will send a notice of electronic filing to the following counsel of record listed below:

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